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Comparative Tolerability of Paracetamol, Aspirin and Ibuprofen for Short-Term Analgesia in Patients with Musculoskeletal Conditions: Results in 4291 Patients

J-M. Le Parc[1], E. Van Ganse[2], N. Moore[3], R. Wall[4], H. Schneid[5] and F. Verrière[5]

[1]Hôpital Ambroise Paré, Boulogne-Billancourt; [2]Hôpital Edouard Herriot, Lyon; [3]Université Victor Segalen, Bordeaux, France; [4]Boots Healthcare International, Nottingham, UK; [5]Boots Healthcare, Levallois Perret, France

Abstract: The aim of this blinded, randomised, multicentre study was to compare the tolerability of aspirin, paracetamol and ibuprofen in common pain resulting from musculoskeletal conditions (MSC) in general practice with patients with other non-MSC pain conditions. Patients took aspirin, paracetamol (both up to 3g daily) or ibuprofen (up to 1.2g daily) for up to 7 days. The main outcome was the rate of significant adverse events (SGAE). Four thousand two hundred and ninety one patients with MSC were evaluable (1436 aspirin, 1423 paracetamol, 1432 ibuprofen) and 4101 (95.5%) were per-protocol. A group of 4342 patients included for other (non-MSC) mild to moderate pain conditions was used for comparison. In the MSC group, SGAE were reported by 20.5% of patients with aspirin, 17.0% with paracetamol and 15.0% with ibuprofen. Ibuprofen was statistically equivalent to paracetamol and better tolerated than aspirin ($p < 0.000l$). Ibuprofen was associated with fewer digestive system AE (4.4%) than aspirin (8.6%, $p < 0.000l$) and paracetamol (6.5%, $p < 0.02$). The non-MSC group showed similar inter-treatment differences, but experienced fewer SGAE. No serious digestive events were observed with any of the three treatments in either group. These results show that in patients with mild to moderate pain resulting from MSC, ibuprofen given in OTC doses for 6 days is as well tolerated as paracetamol and better tolerated than aspirin.

Correspondence and offprint requests to: Jean-Marie Le Parc, Hôpital Ambroise Paré, 9 Avenue Charles De Gaulle, 92 104 Boulogne Billancourt, France. Tel: 33 1 49 09 56 75; Fax: 33 1 49 09 58 65; E-mail: jean-marie.leparc@apr.ap-hop-paris.fr

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Introduction

Musculoskeletal conditions (MSC) are among the most frequent health problems in the developed world, with back pain, degenerative arthritis and soft tissue rheumatism being the most commonly reported [1]. These conditions are characterised by recurrent pain episodes of mild to moderate intensity, a favourable natural history and a need for symptomatic treatment. Analgesics and self-management are recommended as the first line of treatment [2].

The most widely used are over-the-counter (OTC) analgesics, i.e. aspirin, paracetamol and ibuprofen. There is little information concerning the relative tolerability profiles of these medications when used to treat common pain conditions, and no data from prospective studies are available. It was to address this issue that a large-scale study in general practice (the PAIN study) was conducted [3], showing that the tolerability of ibuprofen was equivalent to that of paracetamol and better than that of aspirin. Nearly half the patients in that study were treated for MSC (muscle, joint, tendon or ligament pain, or backache), and so it is of interest to compare the tolerability of the three drugs in patients with MSC, and to establish whether there are any differences in tolerability compared to patients with non-MSC pain indications, such as headache, sore throat and symptoms of cold and flu.

Patients and Methods

The PAIN study was a randomised, multicentre, blinded parallel-group multiple-dose study conducted by general practitioners (GPs) in France and approved by the ethical committee of Ambroise Paré hospital. The methodology used has been previously described [3]. It was designed to compare the tolerability of three commonly used analgesics, and was not powered to detect serious gastrointestinal (GI) adverse events. Treatment randomisation was to one of three groups: ibuprofen 200 mg, paracetamol 500 mg or aspirin 500 mg. Each patient (with either MSC or non-MSC pain) was prescribed up to six tablets per day (similar tablets without trademarks) for up to 7 days. Patients recorded on diary cards the study medication taken and all adverse events (AE) and their severity. Physicians called the patient on the day after the start of treatment to ensure understanding of the study, adherence to the protocol, and to record early adverse events. They called again between days 7 and 9 to clarify adverse events and to ensure return of the diary.

The primary outcome measure was the number of patients with at least one significant AE (SGAE), defined as serious, severe or moderate, resulting in a second physician consultation or discontinuation of treatment.

The secondary outcome measures were adverse events by COSTART body systems and terms; all AE and distribution of AE (serious, severe and moderate); AE in patients over 65 years; and patients' global opinion of treatment.

Aspirin and ibuprofen were compared using a χ^2 test to establish whether there was a difference between the groups using the evaluable population. Ibuprofen and paracetamol were compared in the per-protocol population to establish equivalence by means of a one-sided 96.5% confidence interval (CI) on the absolute differences in AE incidence. Standard 95% CIs for the absolute differences are also presented.

Results

There were 4291 evaluable patients with MSC who were randomised (1436 to aspirin, 1432 to ibuprofen and 1423 to paracetamol); 4101 (95.5%) patients adhered to the protocol (per-protocol population). The reasons for protocol deviation were distributed equally between patients who took a forbidden medication and errors in treatment allocation procedures. The indications were typical of the common MSC treated by GPs: muscle, joint, tendon or ligament pain (2786 patients, 64.9%), backache (1368 patients, 31.9%) and other conditions (137 patients, 3.2%).

A group of 4342 evaluable patients with other (non-MSC) indications such as cold/flu (1705 patients, 39.3%), sore throat (990 patients, 22.8%), headache (892 patients, 20.5%), toothache (341 patients, 7.9%), dysmenorrhoea (179 patients, 4.1%) and various other pain conditions (235 patients, 5.4%) was included for comparison purposes.

The baseline characteristics of the MSC group are shown in Table 1. There were no differences between treatment groups in the incidence of concomitant disease, history of GI disease, use of concomitant medication or mean duration of treatment.

Compared with non-MSC patients, patients with MSC were generally older, with a higher proportion of male patients. The MSC patients had a similar previous history of GI disease and total use of concomitant medication as the non-MSC group, but significantly more had concomitant disease ($P<0.0001$). The mean duration of treatment was longer in the MSC group (6.0 +/− 1.6 days) than in the non-MSC group (5.1 +/− 2.1 days) (Table 1).

Primary Outcome

In patients with MSC, significant adverse events (SGAE) were reported in the evaluable population by 20.5% of patients treated with aspirin, 17.0% of those with paracetamol and 15.0% of those with ibuprofen (Table 2). The absolute difference (95% CI) in SGAE with ibuprofen compared with aspirin was −5.5 (−8.3, −2.7) and compared with paracetamol −2.0 (−4.7, 0.7). Ibuprofen was as well tolerated as paracetamol and significantly better tolerated than aspirin ($P<0.0001$). The per-protocol population gave similar results. Compared with the MSC group, the non-MSC group showed similar intertreatment differences, although it experienced significantly fewer SGAE ($P<0.001$) (Table 2).

Table 1. Baseline characteristics of MSC patients and comparison with non-MSC population

	Ibuprofen (n = 1432)	Aspirin (n = 1436)	Paracetamol (n = 1423)	Total MSC population (n = 4291)	Non-MSC population (n = 4342)
Mean age, years (SD)	47.3 (14.8)	47.8 (14.7)	47.6 (14.6)	47.6 (14.7)	39.5 (13.7)
Male n (%)	625 (43.7)	630 (43.9)	635 (44.7)	1890 (44.1)	1721 (39.7)
Female n (%)	804 (56.3)	806 (56.1)	786 (55.3)	2396 (55.9)	2613 (60.3)
Concomitant disease n (%)	435 (30.4)	425 (29.6)	416 (29.2)	1276 (29.7)	902 (20.8)
History of GI disease n (%)	67 (4.7)	72 (5.0)	54 (3.8)	193 (4.5)	178 (4.1)
Concomitant medication n (%)	613 (42.8)	620 (43.2)	622 (43.7)	1855 (43.2)	2003 (46.1)
Mean treatment duration, days (SD)	6.0 (1.6)	5.9 (1.6)	6.0 (1.5)	6.0 (1.6)	5.1 (2.1)

Table 2. Adverse events by intensity and by COSTART body systems and terms for MSC population

	Ibuprofen (%)	Aspirin(%)	Paracetamol(%)	Aspirin vs Ibuprofen (*P*)	Ibuprofen vs Paracetamol
Intensity					(1)
Significant AE	15.0 (12.3)[2]	20.5 (16.8)[2]	17.0 (12.0)[2]	<0.0001	0.47
Total AE	21.9	28.9	24.9	<0.0001	−0.12 (*P*<0.035)
Severe AE	3.8	5.7	3.7	<0.02	1.41
Moderate AE	9.4	13.4	12.2	<0.001	−0.80 (*P*<0.007)
Systems/terms				(3)	(3)
Body as a whole	8.2 (5.8)[2]	11.9 (8.3)[2]	9.7 (5.9)[2]	<0.001	NS
Abdominal pain	3.1 (2.4)[2]	7.9 (5.6)[2]	4.8 (2.9)[2]	<0.0001	<0.02
Digestive system	4.4 (3.6)[2]	8.6 (5.7)[2]	6.5 (4.1)[2]	<0.0001	<0.02
Dyspepsia	1.7 (1.1)[2]	4.0 (2.3)[2]	3.2 (1.3)[2]	<0.001	<0.01
Nervous system	2.8 (1.0)[2]	2.2 (1.8)[2]	3.0 (0.9)[2]	NS	NS

[1] Equivalence is concluded if the upper limit of the 96.5% confidence interval of the difference in incidence between ibuprofen and paracetamol is < 2.7%. A value less than zero means a statistically significant difference in favour of ibuprofen.
[2] Rates of SGAE for non-MSC group in parentheses. The differences between the MSC and non-MSC groups are statistically significant (*P*<0.001).
[3] *P* value, comparison between treatment groups for MSC population. Significance level set at 0.035. *P* values quoted are two-tailed χ^2 tests. No adjustments have been made for multiple comparisons.

Secondary Outcomes

For total, severe and moderate AE, there were significantly higher percentages of MSC patients in the aspirin than in the ibuprofen group, and either comparable or significantly lower percentages of MSC patients in the ibuprofen than in the paracetamol group (Table 2).

The SGAE coded by COSTART body system and term are presented in Table 2. More patients with MSC reported SGAE for the body as a whole (which includes abdominal pain) when treated with aspirin than with ibuprofen (*P*<0.001) or paracetamol. Similarly, ibuprofen was associated with statistically significantly fewer digestive system SGAE than was aspirin (*P*<0.0001) or paracetamol (*P*<0.02). Statistically significant differences between ibuprofen and aspirin, and between ibuprofen and paracetamol, were also found for abdominal pain and for dyspepsia.

Compared with non-MSC patients, those treated for MSC reported significantly more severe and moderate AE (data not shown), and SGAE for the body as a whole, digestive system, nervous system, abdominal pain and dyspepsia (Table 2) (all *P*<0.001).

There were three cases of non-serious GI bleeding in the MSC group: two patients on paracetamol and one on aspirin reported rectal haemorrhage; one patient on aspirin had peptic ulcer. In the non-MSC group, two patients on paracetamol reported haematemesis and one patient on aspirin reported rectal haemorrhage.

In patients over 65 years (*n* = 632, 14.7%) with MSC, the rates of those with at least one SGAE were 19.0% and 18.3% for ibuprofen and paracetamol, respectively, and higher for aspirin (22.8%). Rates of digestive system SGAE were 6.2% for ibuprofen, 8.5% for paracetamol and 10.7% for aspirin. In the smaller number of patients (*n* = 232, 5.3%) over 65 years in the non-MSC group, the SGAE rates were even higher for aspirin (36.9%), but similar for ibuprofen (12.5%) and paracetamol (12.6%).

The global evaluation of treatment was rated good or excellent by 66.4% of MSC patients on ibuprofen, 59.5% of those on paracetamol and 59.7% of those on aspirin (*P*<0.0005 ibuprofen vs. aspirin or paracetamol). The treatments were rated more highly by the non-MSC group (ibuprofen 81.9%, paracetamol 78.6% and aspirin 77.5%).

Discussion

Assessment of the tolerability of OTC analgesics for the treatment of mild to moderate pain requires studies designed to elicit adverse event data directly from patients. The PAIN study [3] was the first prospective blinded tolerability study based mainly on patients' AE reports and was designed to examine tolerability in a variety of common pain indications. The doses used were those approved for OTC analgesic treatment in France and in other countries, and the treatment prescription reflected the usual conditions of use by patients with mild to moderate pain conditions. As one of the most frequent indications for short-term analgesic treatment is pain resulting from MSC, a separate analysis of this group was of prime interest.

Compared to non-MSC patients, those in the MSC group were older (with 15% over 65 years) and had significantly more concomitant disease, but did not differ in terms of use of concomitant medication and previous GI disease. As expected, the duration of treatment was longer in MSC patients, reflecting the pain profile of rheumatic conditions compared with that of headache, for example. More patients with MSC had SGAE than did those without MSC, although in both groups ibuprofen was significantly better than aspirin, and there was equivalence between ibuprofen and para-

cetamol. For other types of events, including digestive system events and the commonest events, abdominal pain and dyspepsia, ibuprofen was superior to aspirin and had a significantly lower event rate than paracetamol. In patients over 65 years with MSC, SGAE were on average more frequent by 2.5% than in younger patients, but for both digestive and total significant events ibuprofen was comparable with paracetamol and better tolerated than aspirin.

The good GI tolerance of ibuprofen is of particular interest. The prevalence of MSC, the GI tolerance of NSAIDs and the pattern of use of OTC analgesics are issues of epidemiological importance. For example, 15% of adults aged 20–64 in the USA suffer low back pain, equivalent to 26 million patients requiring intermittent analgesic treatment; in the population over 65 years, 6 million have low back pain [1,2,4]. The results of this study suggest that in patients with MSC ibuprofen can be considered as a first-line analgesic for short-term use in accordance with the usual contraindications (previous GI bleeding or major risk factors for GI bleeding).

In conclusion, this study shows that, at the recommended OTC analgesic doses, in patients with pain resulting from common musculoskeletal conditions observed in general practice, ibuprofen is as well tolerated as paracetamol, and better tolerated than aspirin, when treatment is taken for a period of 6 days. For digestive system events, ibuprofen was not only superior to aspirin but was also associated with a significantly lower event rate than paracetamol. As a longer duration of treatment by GPs and rheumatologists of certain MSC, such as osteoarthritis and chronic back pain, may be necessary, further studies of 4–6 weeks' treatment are needed to confirm these findings.

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